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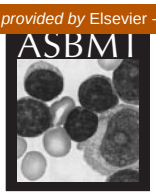

Early Antithymocyte Globulin Therapy Improves Survival in Patients With Steroid-Resistant Acute Graft-Versus-Host Disease

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ABSTRACT

Second-line therapies for steroid-resistant acute GVHD have been used with limited success. We have reviewed the responses of 79 hematopoetic stem cell transplant (HSCT) patients uniformly treated from 1990-1998 with equine antithymocyte globulin (ATG) for steroid-resistant acute GVHD, defined as progression of acute GVHD after 4 days of treatment with prednisone or no improvement of acute GVHD after 7 days of treatment with prednisone. Patients received HSCT from 34 related (32 matched sibling/2 partially matched) and 45 unrelated (14 HLA-A, -B, -DRB1 matched/31 partially matched) donors. Prior to ATG therapy, severe (grade III-IV) GVHD was observed in 34 patients (43%). Organs involved included skin in 81% of patients, lower GI tract in 52%, upper GI tract in 28%, and liver in 11%. Treatment consisted of 1-5 courses (median, 2 courses) of ATG (15 mg/kg per dose bid × 5 days) given for a median of 16 days (range, 5 to 44 days) after the onset of GVHD. All patients continued to receive prednisone, 60 mg/m^2 per day (or methylprednisolone IV equivalent), plus CSA (75%) or tacrolimus (4%). At day 28 of treatment, overall improvement was observed in 54% of patients; durable (≥28 days) complete response was observed in 20% of patients, and partial response was observed in 34% of patients. In multivariate analysis, patients with CML or a malignant disease other than acute leukemia had a greater likelihood of overall response than did those with nonmalignant diseases. Patients with acute skin GVHD (with or without other organ involvement) responded most frequently. Chronic GVHD developed in 51% of patients by 1 year after HSCT. One patient developed EBV lymphoproliferative disease. For the entire cohort, the probability of survival at 1 year was 32% (95% CI, 22%-42%). In multivariate analysis, factors associated with better survival included earlier onset of acute GVHD, shorter time from initial treatment for GVHD to treatment with ATG, and the use of non–T-cell–depleted stem cell grafts. These data suggest that treatment with ATG can be an active therapy, especially in patients with skin GVHD and early signs of steroid resistance.

KEYWORDS

Acute GHVD • ATG • Steroid resistance • Hematopoietic cell transplantation • Unrelated donor

INTRODUCTION

Acute graft-versus-host disease (GVHD) remains a significant cause of morbidity and mortality after allogeneic hematopoietic stem cell transplantation (HSCT). High-dose steroids for acute GVHD induce a durable remission in 50% of cases [1-6]. For those patients who do not achieve remission, a variety of second-line therapies have been used with success in approximately 10% to 30% of cases [2,4,7-10]. Administration of antithymocyte globulin (ATG) as second-line therapy has been studied in HSCT recipients in the 1970s and 1980s, and responses were demonstrated in 20% to 50% of patients with steroid-resistant acute GVHD [4,7,8]. Over the past decade, the nature of HSCT has changed substantially with the increased use of alternate donor sources, changes in GVHD prophylaxis, and supportive care. There have been few reports addressing the use of ATG in recent patients.

To assess the impact of ATG on steroid-resistant acute GVHD in the 1990s, we retrospectively analyzed the clinical response and survival of 79 HSCT patients, uniformly

treated at a single institution from 1990 to 1998 on protocol with equine ATG (15 mg/kg per dose bid × 5 days) for steroid-resistant acute GVHD.

PATIENT POPULATION AND METHODS

Patients

Clinical and laboratory data were retrieved from the University of Minnesota Bone Marrow Transplant Database, which systematically and prospectively collects data on all consecutive HSCT patients at our institution. From August 1990 to November 1998, 1016 patients received allogeneic HSCTs at the University of Minnesota. All protocols for transplantation and treatment of GVHD were reviewed and approved by the Institutional Review Board at the University of Minnesota. All patients and/or parents of patients gave informed consent. Of the 1016 patients, 645 (63%) developed acute GVHD, and 202 received secondary immunosuppressive therapy for steroid-resistant acute GVHD. Of these 202 patients, 97 were enrolled in a randomized trial of ATG as initial therapy for GVHD [6], and a subset of 79 allogeneic HSCT recipients, who developed steroid-resistant acute GHVD and who did not receive ATG as initial therapy, were enrolled in this study.

Patient characteristics, including underlying disease, type of donor, and type of GVHD prophylaxis are shown in Table 1. Patients received their HSCTs from August 1990 to November 1998 and were followed for a median of 6 years (range, 1.0-9.0 years). HSCT sources included bone marrow (BM; n = 73), peripheral blood stem cells (PBSC; n = 4), and umbilical cord blood (UCB; n = 2). Details of the preparative therapy and GVHD prophylaxis that were used, as well as supportive therapy techniques, have been previously reported [11,12]. Eighty-four percent of patients received total body irradiation (TBI)-based regimens and 16% of patients received chemotherapy-alone regimens. GVHD prophylaxis consisted of cyclosporin A (CSA)-based therapy for 67% of patients, T-cell depletion for 13% of patients, methotrexate-based therapy (no CSA) for 18% of patients, and tacrolimus for 2% of patients. Patients with T cell–depleted grafts were older, with a median age of 34 years (range, 10-52 years) compared to patients with unmanipulated grafts with a median age of 24 years (range, 0.4-52 years).

Table 1. *Clinical Features of Patients with Acute GVHD Treated With ATG**

Features	n (%)
Male:female ratio	50:29 (63:37)
Male donor/male recipient	34 (43)
Male donor/female recipient	16 (20)
Female donor/male recipient	16 (20)
Female donor/female recipient	13 (17)
Age median (range), y	27 (0.4-51)
Diagnosis	
ALL	17 (22)
AML	11 (14)
CML	28 (35)
MDS	7 (9)
Other malignancy	2 (2)
Metabolic disorder	7 (9)
Aplastic anemia/bone marrow failure	5 (6)
Immune deficiency	2 (3)
Donor type	
Matched related	32 (41)
Mismatched related	2 (3)
Matched unrelated	14 (18)
Mismatched unrelated	31 (39)
Preparative therapy	
Cyclophosphamide and TBI	56 (71)
TBI with other chemotherapy	10 (13)
Chemotherapy alone	10 (13)
Chemotherapy and ATG	3 (4)
GVHD prophylaxis	
CSA/MTX	46 (58)
CSA/prednisone ± other	7 (9)
MTX/ATG/prednisone	10 (13)
Ex vivo T-lymphocyte depletion	10 (13)
Tacrolimus	2 (3)
MTX alone	4 (5)

*MDS indicates myelodysplastic syndrome.

Diagnosis and Staging of GVHD

Acute GVHD was diagnosed clinically with histological confirmation whenever possible. Symptoms of acute GVHD were graded by standard clinical criteria [3,13], modified to include upper gastrointestinal (GI) acute GVHD per the GVHD consensus conference [14,15], and by the IBMTR severity index [16]. Grade of GVHD refers to clinical (not histologic) grade throughout this report. Initial score was defined as the maximum stage in each organ during a 15-day window (day –10 to day 5) around the initiation of ATG therapy. Real-time staging of each organ was determined by the attending physician, supported by laboratory and clinical information abstracted from the medical records. The overall grade was determined by a computer algorithm, incorporating all available clinical GVHD organ staging data, centrally reviewed by the GVHD Grading Committee at our center (S.M.D. and D.J.W.), and prospectively recorded in the University of Minnesota BMT Database.

Therapy for GVHD

Primary treatment of acute GVHD consisted of daily divided-dose prednisone, 60 mg/m^2 PO (or methylprednisolone IV equivalent, 48 mg/m^2), plus CSA in 53 patients (67%) or tacrolimus in 2 patients (3%). In addition, patients with acute skin GVHD were treated with topical 0.1% triamcinolone cream or 1% hydrocortisone cream (for facial rash) tid. Steroid-resistant acute GVHD was defined as progression of acute GVHD after 4 days of treatment with prednisone or no improvement of acute GVHD after 7 days of treatment with prednisone. Patients with limited skin (grade I) acute GVHD were eligible for this study if they failed to improve after 7 to 14 days of prednisone therapy.

For steroid-resistant acute GVHD, all patients received equine ATG (ATGAM; Pharmacia, Peapack, NJ), 15 mg/kg per dose IV over 3 hours bid for 5 days for a total of 10 doses. Premedications consisted of acetaminophen and diphenhydramine. Prednisone 30 mg/m^2 PO (or methylprednisolone IV equivalent, 24 mg/m^2) was given with each dose of ATG and then continued for at least 7 days. Patients with acute skin GVHD continued to receive treatment with

0.1% triamcinolone cream to the body and 1% hydrocortisone cream to the face. If a response to ATG was observed, patients continued therapy with single-dose prednisone, 60 mg/m^2 per day PO, for 7 days and then commenced a taper of steroids over 8 weeks [15]. If no response to ATG was observed after 7 to 10 days, or progression of GVHD occurred after 14 days, the ATG course was repeated.

Patients received supportive care, which included ongoing prophylaxis for bacterial infections (250 mg penicillin V potassium PO, bid), fungal infections (clotrimazole, nystatin, or fluconazole), *Pneumocystis carinii* pneumonia (trimethoprim-sulfa, double strength bid every Monday and Tuesday), and cytomegalovirus (CMV) (800 mg acyclovir PO 5 times per day). Children received the same prophylaxis appropriately dose-adjusted for weight.

At initiation of ATG treatment, overall GVHD grade was grade I in 7 patients (9%), grade II in 38 patients (48%), grade III in 30 patients (38%), and grade IV in 4 patients (5%). The 7 patients with overall grade I GHVD had steroid-resistant stage II skin GVHD, which failed to improve after 7 to 28 days of prednisone therapy. Maximum initial GVHD stage in each organ for each patient is shown in Table 2. Median time to onset of GVHD from day of HSCT was 28 days (range, 8-91 days). Median time to treatment with ATG after initiation of initial steroid therapy was 16 days (range, 5-79 days). Median time to treatment with ATG from day of HSCT was 48 days (range, 15-105 days). The total number of courses of ATG treatment was 1 for 31 patients (39%), 2 for 29 patients (37%), 3 for 9 patients (11%), 4 for 6 patients (8%), and 5 for 4 patients (5%).

Measurement of GVHD Response to ATG Administration

The day 28 response was determined from the maximum acute GVHD grade observed 28 days (±14 days) after the first course of ATG treatment was initiated. Response to therapy was evaluated by the attending physician of the transplantation service and prospectively recorded in the University of Minnesota BMT Database at treatment days 7, 14, 21, 28, and 42 by determining the GVHD clinical stage score for each time point (±3 days) [5]. Complete response (CR) was defined as the complete resolution of all acute GVHD symptomatology in all organs. To be considered a CR, this score had to be maintained for 28 days (ie, beyond day 56 after initiating ATG therapy) without the patient receiving additional treatment. Partial response (PR) was defined as durable (≥28 further days) improvement in GVHD stage in all initial GVHD target organs, without complete resolution and without worsening in any other GVHD target organs. No response (NR) was defined as the same grade of GVHD or progression of GVHD in any organ, or death before day 28 after ATG. Patients who received additional ATG courses or a second salvage regimen were considered nonresponders. Progression was defined as worsening GVHD in ≥1 organ with or without amelioration in any organ. For assessment of treatment response, a GVHD-stage score was determined for each patient, as previously described [2]. This stage score represented the sum of each acute GVHD organ stage (0 to 4) plus 1 point for upper GI involvement and thus had a maximum possible score of 13.

Table 2. *Maximum Initial GVHD Stage at the Onset of ATG Therapy**

	0	1	2	3	4
Skin	15 (19%)	8 (10%)	13 (17%)	42 (53%)	1 (1%)
Liver	70 (89%)	1 (1%)	3 (4%)	3 (4%)	2 (3%)
Rectal	38 (48%)	13 (17%)	8 (10%)	17 (22%)	3 (4%)
Upper GI	57 (72%)	22 (28%)			

*Data are n (%). Maximum stage during a 15-day window (day –10 to day 5) around the initiation of ATG therapy.

Statistical Analysis

The major end points of this study were response to GVHD therapy at day 28 after treatment, and survival. Statistical analysis of response to therapy was performed using Pearson's chi-square test. The independent effect of study variables on response was determined using multivariate logistic regression [17].

Survival was measured from the time of initiation of ATG therapy. The Kaplan-Meier method was used to estimate survival with 95% confidence intervals [CIs] derived from standard errors. Comparison within study cohorts was completed by the log-rank statistic. Cox regression was used to determine the independent effect of these factors [18]. Cumulative incidence curves were calculated to estimate the incidences of chronic GVHD and infectious complications. Deaths from other causes were treated as competing risks [19].

Study variables included age, year of transplantation, sex, sex match, diagnosis, type of donor (related, matched unrelated, mismatched unrelated), CMV serostatus of the patient and donor, GVHD prophylaxis regimen, conditioning regimen, initial grade of acute GVHD, time to onset of acute GVHD, time to therapy, and type of organ involvement. The effect of response to therapy on survival was also investigated as a time-dependent covariate. *P* values were not adjusted for multiple comparisons, so nominally statistically significant results should be interpreted with caution.

RESULTS

Response

Of the 79 patients treated with ATG, overall durable improvement (CR + PR) was observed in 43 patients (54%) by day 28 after initiation of ATG. CR was achieved in 16 patients (20%), PR in 27 patients (34%), and NR in 33 patients (42%), and 3 patients (4%) were unevaluable due to early death.

Various patient characteristics and transplantation conditions were analyzed for their association with clinical response to ATG therapy by day 28. In univariate analysis, only a nonmalignant diagnosis was associated with a statistically significant lower likelihood of CR/PR ($P = .04$). CR or PR was achieved in 21 of the 34 related donor recipients (62%; 95% CI, 46%-78%) compared to 22 of 45 unrelated donor recipients (48%; 95% CI, 33%-63%) ($P = .26$). CR or PR was achieved in 39 of 66 patients conditioned with TBI (59%; 95% CI, 47%-71%) compared with 4 of 13 patients conditioned with non-TBI preparative therapy (31%; 95% CI, 6%-56%) ($P = .06$). There was no association between CR/PR following ATG treatment and patient age, sex, sex

match, year of transplantation, CMV serostatus, GVHD prophylaxis, or time between first-line therapy with steroids and initiation of ATG treatment. In addition, CR/PR to ATG was not associated with the initial grade of GVHD, regardless of which scoring system was used [14,16].

The response to ATG treatment among patients with various combinations of organ involvement was analyzed. Patients with acute skin GHVD (with or without other organ involvement) responded most frequently. Of the 64 patients with skin involvement, 39 patients (61%) achieved CR/PR versus 4 of 15 patients (27%) without skin involvement (P = .02). Response rates did not differ between patients with only skin involvement and patients with skin plus other organ involvement. The number of organs involved and stage of organ involvement were not prognostic indicators of response to ATG. In addition, organ score was not predictive of response to GVHD treatment.

The clinical factors relevant to the likelihood of achieving CR/PR were examined in a multivariate analysis (Table 3). A diagnosis of chronic myelogenous leukemia (CML) or a malignant disease other than acute leukemia was associated with a greater likelihood of CR/PR, compared to a diagnosis of nonmalignant disease. In addition, patients who had acute GVHD skin involvement were significantly more likely to respond to ATG therapy than were those without skin involvement. Type of donor, initial GVHD grade, and time from steroid therapy to ATG initiation were not significant predictors of response to ATG.

Chronic GVHD

Forty of the 79 patients developed chronic GVHD by 1 year after HSCT, resulting in a cumulative incidence of 53% (95% CI, 39%-67%). By 1 year, 41% of patients had died from causes other than chronic GVHD (95% CI, 31%-51%). Chronic GVHD developed in 4 of the 7 patients with initial grade I GVHD (57%; 95% CI, 24%-90%), 20 of the 38 patients with initial grade II GVHD (53%; 95% CI, 33%-73%), 14 of 30 patients with initial grade III GVHD (47%; 95% CI, 26%-68%), and 2 of 4 patients with grade IV GVHD (50%; 95% CI, 1%-99%) (P = not significant [NS]). Eight of 16 patients who had CR to ATG later developed chronic GVHD (50%; 95% CI, 22%-78%), 14 of 27 who had PR later developed chronic GVHD (52%; 95% CI, 30%-74%), and 18 of 33 who had NR later developed chronic GVHD (55%; 95% CI, 35%-75%) (P = NS).

Table 3. *Factors Associated With Complete/Partial Response to ATG for Acute GVHD: Multivariate Logistic-Regression Analysis*

Factor	Odds Ratio of Response (95% CI)	P
Diagnosis		
Nonmalignancy	1.0	
Acute leukemia	2.3 (0.6-9.4)	.26
CML	5.7 (1.3-24.2)	.02
Other malignancy*	8.6 (1.2-64.2)	.04
Skin Involvement		
No	1.0	
Yes	4.4 (1.2-16.5)	.03

*Other malignancy indicates MDS (n = 7), juvenile myelomonocytic leukemia (n = 1), or non-Hodgkin's lymphoma (n = 1).

Infectious Complications

Within the first 100 days after transplantation, 29 patients developed bacterial infections (37%; 95% CI, 26%-48%), from which 2 died; 14 developed fungal infections (18%; 95% CI, 10%-26%), from which 6 died; and 8 developed CMV infections (10%; 95% CI, 4%-16%), from which none died. Only 1 patient developed Epstein-Barr virus (EBV) lymphoproliferative disease after ATG therapy.

Survival

In the entire cohort of 79 patients, 25 are alive between 1 and 9 years after treatment, with a Kaplan-Meier projected estimate of 32% survival at 1 year (95% CI, 22%-42%). Various clinical factors were examined for their association with improved survival (Table 4). The probability of survival

Table 4. *Clinical Risk Factors Associated With Survival*

	n	No. of Patients Who Died	1 year*	P†
Overall	79	54	32%	
Age				
<18 y	34	21	38%	.16
≥18 y	45	33	21%	
Diagnosis				
Acute leukemia	28	18	36%	.63
CML	28	20	29%	
Other malignancy	9	7	22%	
Nonmalignant	14	9	36%	
Type of HSCT				
Related donor	34	22	35%	.10
Matched URD	14	12	14%	
Mismatched URD	31	20	35%	
GVHD prophylaxis				
MTX-containing	14	8	43%	.11
CSA-containing	53	35	34%	
T-cell depletion	10	9	10%	
Conditioning Prep				
TBI	66	47	29%	.23
Non-TBI	13	7	46%	
Initial overall GVHD				
1	7	5	29%	.29
2	38	22	42%	
3-4	34	27	21%	
Skin involvement				
No	15	13	13%	.12
Yes	64	41	36%	
Time to onset of GVHD				
<4 wk	44	28	36%	.24
≥4 wk	35	26	26%	
Time between steroids/ATG				
≤2 wk	37	20	46%	.05
>2 wk	42	34	19%	
Response to ATG				
CR	16	10	38%	.54
PR	27	17	37%	
NR	33	24	27%	
Overall response to ATG				
CR, PR	43	27	37%	.27
NR	33	24	27%	

*1-year survival from initiation of ATG therapy.

†P values reflect log-rank statistical comparison of survival up to 1 year after initiation of ATG therapy.

12 months after ATG was similar in related and unrelated donor recipients, 35% (95% CI, 19%-51%) and 29% (95% CI, 16%-42%), respectively (P = .58).

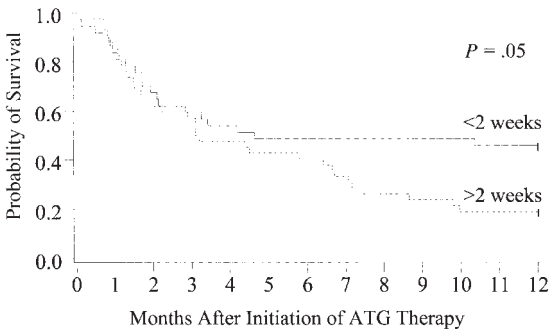
Recipients of T cell–replete grafts had a higher probability of survival at 1 year (36% [95% CI, 25%-47%]) than did recipients of T cell–depleted grafts at 1 year (10% [95% CI, 0%-28%]) (P = .04). Other clinical factors, including age and sex of recipient, year of transplantation, underlying diagnosis, preparative therapy, or CMV serostatus, had no association with improved survival.

Using either GVHD scoring system, initial overall GVHD grade was not associated with improved survival. With the GVHD consensus conference scoring system [14], probability of survival at 1 year after ATG therapy for patients with grade I-II GVHD and grade III-IV GVHD was 40% (95% CI, 26%-54%) and 21% (95% CI, 8%-34%) (P = .14), respectively. In addition, the number of organs involved was not a prognostic factor, with the probability of survival in patients with 1, 2, or >2 involved organs being 33%, 33%, and 23%, respectively (P = NS). GVHD-stage score was also not predictive of survival.

Patients in whom ATG therapy was initiated within 2 weeks of steroid treatment had a higher probability of survival than did patients with a longer period between treatment regimens (46% [95% CI, 30%-62%] versus 19% [95% CI, 7%-31%]; P = .05) (Figure 1). No association was observed between number of ATG courses and survival. Probability of 1-year survival for patients who received 1 course of ATG was 42% (95% CI, 13%-59%) and 25% (95% CI, 13%-37%) for patients who received 2 or more courses (P = .26).

Perhaps surprisingly, achievement of CR by day 28 (±14 days) did not predict improved survival. Probability of survival at 1 year was 38% (95% CI, 14%-62%) for the 16 patients with CR and 32% (95% CI, 20%-44%) for the 60 patients with PR or NR (P = .73). Similarly, survival was not affected by overall response (CR + PR). The probability of the 43 patients with overall response surviving at 1 year after ATG therapy was 37% (95% CI, 23%-51%) compared to 27% (95% CI, 12%-42%) for nonresponders (P = .27).

In a multivariate analysis, the use of a non–T cell–depleted stem cell graft (ie, unmanipulated BM, PBSC, or UCB), shorter time from transplantation to onset of acute GVHD, and shorter time from initial steroid treatment to ATG were independently associated with greater survival (Table 5).



Probability of survival stratified by time to initiation of ATG therapy.

Causes of Death

The primary cause of death was GVHD in 48 patients (89%) and relapse in 6 patients (11%). Infections were a contributing cause in 36 deaths (67%).

DISCUSSION

Successful treatment of steroid-resistant acute GVHD is difficult. In this report, we observed an overall improvement in 54% of patients receiving ATG for steroid-resistant acute GVHD and a durable CR in 20% of patients. This outcome is better than those reported in 2 previous series examining the role of ATG in steroid-resistant acute GVHD. The Seattle group reported on a large series of patients who received secondary treatment for acute GVHD, including 94 patients who received ATG. Of the 79 evaluable patients, CR was observed in 8% of patients and CR + PR in 30% of patients [7]. Recently, Khoury et al. reported 58 patients with steroid-resistant acute GVHD treated with ATG [20]. Of the 52 evaluable patients, CR was observed in 8% of patients and CR + PR in 31% of patients. In the Khoury series, the poorer outcome may be due in part to the large percentage of patients (94%) with severe GVHD (IBMTR C and D). In our present series, 43% of patients had severe GVHD (grade III-IV). In addition, the durability of responses to ATG was not clarified in the earlier series. Our results are consistent with reports on the use of other second-line agents for acute GVHD, including steroids and monoclonal antibodies [2,7,9,10]. Interestingly, our results are similar to those observed when ATG is used as primary therapy for acute GVHD [6,8,21].

Response to ATG therapy was observed most often in patients with skin GVHD and early recognition of steroid resistance, suggesting that these steroid-resistant patients benefited the most from ATG therapy. Consistent with other studies, patient age [2,4,8], sex [2], type of donor [4,7,8], or GVHD prophylaxis [2,4,7] were not associated with response to ATG. Other studies have demonstrated poorer response rates in those patients with more severe grades of steroid-resistant GVHD [7,8].

In contrast with the current series, we have previously observed favorable survival in association with a response to

Table 5. *Clinical Factors Associated With Mortality in Acute GVHD: Multivariate Analysis*

Favorable Factor	Relative Risk of Death (95% CI)	P
Prophylaxis for GVHD		
No T-cell depletion	**1.0**	**.03**
T-cell depletion	**2.5 (1.1-5.5)**	
Type of donor		
Related	**1.0**	**>.80**
Unrelated	**0.9 (0.5-1.7)**	
Time to acute GVHD (per wk)	**1.2 (1.0-1.4)**	**.05**
Time from initial treatment to ATG (per wk)	**2.1 (1.1-3.9)**	**.02**
Skin involvement		
No	**1.0**	**.26**
Yes	**0.7 (0.4-1.3)**	

second-line acute GVHD treatment. Weisdorf et al. reported CR in 7 of 61 matched sibling–donor (MSD) recipients treated with second-line immunosuppressive therapy for acute GVHD [2]. Five-year probability of survival was 23%, and a CR of acute GVHD was an important predictor of survival [2]. Similarly, Roy et al. observed a 21% CR in 42 recipients of unrelated-donor (URD) transplants, treated with ATG as secondary therapy. Complete and continuing response to therapy was associated with a better survival [4]. In the current series, 60% of patients were recipients of alternate donor stem cells (ie, other than MSD) [4]. Notably, their response to ATG and their survival was similar to the MSD recipients.

We identified few demographic or clinical factors that influenced survival. A longer time from transplantation to the onset of acute GVHD and a longer time from initial steroid treatment to ATG therapy were each independently associated with greater mortality. Because the grade of acute GVHD did not vary with posttransplantation time, this factor did not reflect delay in recognition or treatment of steroid-resistant GVHD.

Over the last 2 decades, studies of supplemental immunosuppression for steroid-resistant acute GVHD have included ATG [9,21], tacrolimus [22], anti-cytokines (interleukin [IL]-1RA [23], anti–IL-2R [24-26], and anti–tumor necrosis factor [27]), anti–T-cell antibodies [9,28-31], or immunotoxins (XOMA [32,33] and daclizumab [10]) with varying but only modest response and usually poor survival. Although ATG is an active agent, improvements in control of GVHD and survival await more effective reagents. Better control of the initial manifestations of acute GVHD would limit the hazards patients face from ongoing GVHD and long-term immunosuppression.

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